Remarks

Formal Matters

Claims 1, 3-8, 16-25, 28-45, and 48-50 remain in this application. Claims 2, 9-15, and 46-47 have been canceled. Claims 18, 19, 21, 28-45 and 48-50 have been withdrawn as the result of an earlier restriction requirement. Claims 1 and 20 are amended. No new matter is added by the amendments.

Support for the amendments is found generally throughout the specification, and specifically at least as indicated below:

Claims 1, 20: turbidity: Example 2, Table 1, page 70, lines 1-3 and lines 14-16, and page 71.

In view of the Examiner's earlier restriction requirement, applicant retains the right to present withdrawn claims 18, 19, 21, 28-45 and 48-50 in a divisional application.

The Rejection Under 35 U.S.C. § 102(e)

Claims 1, 3-8 and 20 are rejected under 35 U.S.C. § 102(e) as being anticipated by US2003/0138417, as evidenced by US2004/0191243.

Specifically, the Examiner asserts that the '417 publication discloses stable, isotonic liquid, pharmaceutical antibody formulations comprising 50 mM histidine buffer, 0.03% polysorbate at pH 6 (Ex. 8, para. 104). The Examiner further asserts that the '417 publication discloses that this pharmaceutical formulation can be used in stabilizing IgE antibody formulations at concentrations greater than 100 mg/ml (abstract, claims 2-3) with about 50-200 mM tonicity modifier such as arginine (para. 52).

This rejection is essentially maintained from the prior Office Action. Applicants had previously argued that US2003/0138417 is not a proper anticipatory reference because: (1) the disclosed of range of 100 mg/ml antibody concentration and greater does not enable the practice of the claimed range of 120-260 mg/ml anti-IgE antibody concentration; and (2) the selection of

arginine hydrochloride as a particularly suitable excipient was not disclosed in the generic disclosure of the '417 reference listing arginine as one of several possible excipients.

Responding to Applicants' initial rebuttal, the Examiner relies upon the newly cited '243 reference to provide evidence that arginine was known specifically as a suitable excipient in antibody formulations. The Examiner dismisses Applicants' comments regarding the '417 disclosure of NaCl excipient as non-enabling by asserting that NaCl is not the claimed subject matter.

In response, Applicants would first like to point out that the Examiner is not fully appreciating Applicants' argument. The Examiner is relying upon the disclosure of "100 mg/ml and greater" to anticipate the claimed range of "120 mg/ml to 150 mg/ml". As is demonstrated by Liu *et al., J. Pharmaceutical Sci.* 94(9): 1928 (2005), the viscosity of antibodies at high concentrations is variable depending upon the antigen specificity. Thus, the properties of a particular antibody in one formulation at 100 mg/ml is not predictive, or "sufficiently specific" of the properties of another at a much higher concentration of 120 - 260 mg/ml. The Examiner has not addressed this point. A proper anticipation rejection requires the disclosure of each and every element of the claimed invention. The generic disclosure of an antibody concentration range of greater than 100 mg/ml does not anticipate the claimed range of 120 - 260 mg/ml for the specific anti-IgE antibodies because the generic disclosure lacks sufficient specificity. The use of the '243 reference in combination with the '417 reference is improper. To support an anticipation rejection; the Examiner can not rely upon a supplemental reference to supply a claim element lacking in the primary reference.

Because the nature of the subject matter involves a claimed range, the Examiner must extrapolate the broad range disclosed in '417 in order to cover the more narrowly range that is limited to a particular class antigen-binding class of antibodies. The point of Applicants' argument concerning NaCl as well as illustrating the other specifically disclosed antibodies (*i.e.*, anti-IL2R, anti-IL12, anti-L-selectin) was to point out that the specific examples of antibody

formulations described in the '417 reference would be inoperable for the claimed antibodies. The Examiner has not addressed this point.

Applicants respectfully request reconsideration and withdrawal of the rejection of Claims 1, 3-8 and 20 are rejected under 35 U.S.C. § 102(e) as being anticipated by US2003/0138417, as evidenced by US2004/0191243.

The First Rejection Under 35 U.S.C. § 103(a)

Claims 1, 16, 17, 22-25 are rejected under 35 U.S.C. § 103(a) as being unpatentable over US 2003/0138417 as evidenced by US 2004/0191243 in view of U.S. Pat. No. 5,994,511.

Specifically the Examiner asserts that the '417 is a proper anticipatory reference and the combined teachings of the references renders the claims obvious.

In response, in light of the preceding arguments, the '417 reference is not a proper anticipatory reference. While the '243 reference does specifically describe arginine as an excipient, this reference does not specifically describe any antibody in a stable liquid formulation of 120 - 260 mg/ml. In fact, most of the specific examples recite antibody concentrations of 50 mg/ml, with the highest concentration specifically described is 100 mg/ml of ABX-IL8, in Examples 12 and 15. While Example 16 of '243 does describe 150 mg/ml after purification, this was only in the context of a viscosity measurement, not for an evaluation of a stable formulation. Moreover, the histidine concentration in this solution was only 5 mM, which is outside the claimed range. The '243 reference does not describe liquid anti-IgE formulations. While the '511 patent teach anti-IgE antibodies, it does not each liquid formulations of such antibodies at a concentration of 120 - 260 mg/ml. As a result, none of the references, in any combination teach, a stable, liquid formulation of (1) anti-IgE antibodies in a concentration of 120 - 260 mg/ml, (2) arginine-HCl in an amount of 50 to 200 mM, (3) histidine in an amount of 10 to 100 mM, (4) polysorbate in amount of 0.01 to 0.1%, further having a pH of 5.5 to 7.0, a kinematic viscosity of about 50 cs or less, an osmolarity ranging from 200 mOsm/kg to 450 mOsm/kg and the claimed turbidity measurement.

The Second Rejection Under 35 U.S.C. § 103(a)

Claims 1, 3-8, 16, 17, 20 and 22-25 are rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 97/26909, in view of U.S.P. 5,994,511.

Specifically, the Examiner asserts that the '909 publication teaches a stable protein formulation comprising 10 mM histidine, 160 mM arginine-HCl, a pH of 7, a protein concentration of about 160 mg/ml and 0.05 % polysorbate. The Examiner further asserts that such a formulation would inherently possess the additional claimed properties of low turbidity, 50 cs or less kinematic viscosity and osmotic pressure from 270 - 328 mOsm.

In response, Applicants respectfully submit that the Examiner is ignoring Applicants point that the anti-IgE antibodies of the invention, when formulated at high concentrations, do not behave in manner similar to that of other antibodies. This fact is supported by the previously supplied Liu et al. reference discussed above. The Examiner has not addressed this point. The '909 reference also does not describe formulations of anti-IgE antibodies comprising a combination of arginine, histidine and polysorbate, which have low turbidity and a viscosity of 50 cs or less. While the '511 patent teach anti-IgE antibodies, it does not each liquid formulations of such antibodies at a concentration of 120 - 260 mg/ml. As a result, none of the references, in any combination teach, a stable, liquid formulation of (1) anti-IgE antibodies in a concentration of 120 - 260 mg/ml, (2) arginine-HCl in an amount of 50 to 200 mM, (3) histidine in an amount of 10 to 100 mM, (4) polysorbate in amount of 0.01 to 0.1%, further having a pH of 5.5 to 7.0, a kinematic viscosity of about 50 cs or less, an osmolarity ranging from 200 mOsm/kg to 450 mOsm/kg and the claimed turbidity measurement.

Applicants respectfully request reconsideration and withdrawal of Claims 1, 3-8, 16, 17, 20 and 22-25 are rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 97/26909, in view of U.S.P. 5,994,511.

Judicially Created Double Patenting Rejection

Claims 1, 3-8, 16, 17, 20 and 22-25 are rejected on the grounds of non-statutory obviousness-type double patenting over claims 1-4, 7-13, 22-27, 31-34, 37-42, 48, 51-56, 58 and 59 of U.S. Patent No. 6,875,432 in view of U.S. 2004/109243.

In response, as this is a provisional rejection, Applicants respectfully request that it be held in abeyance until such time as the claims of otherwise been found to be patentable.

SUMMARY

Claims 1, 3-8, 16-25, 28-45 and 48-50 are pending in the application

If in the opinion of the Examiner, a **telephone conference** would expedite the prosecution of the subject application, the Examiner is **strongly encouraged** to call the undersigned at the number indicated below.

This response/amendment is submitted with a transmittal letter and petition for a 3-month extension of time and fees. In the unlikely event that this document is separated from the transmittal letter or if fees are required, applicants petition the Commissioner to authorize charging our Deposit Account 07-0630 for any fees required or credits due and any extensions of time necessary to maintain the pendency of this application.

Applicants respectfully request that a timely Notice of Allowance be issued in this case.

Respectfully submitted,
GENENTECH, INC.

Date: June 25, 2007

By: _____
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